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MicroRNAs and Androgen Receptor 3′ Untranslated Region: A Missing Link in Castration-resistant Prostate Cancer?

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Abstract

The ligand-activated transcription factor, androgen receptor (AR) plays a central role in the development and progression of prostate cancer. Prostate cancer initiates as an androgen-dependent disease and further accumulation of multiple sequential genetic and epigenetic alterations transform it into an aggressive, castration-resistant prostate cancer (CRPC). The molecular basis of the transition from androgen-dependent prostate cancer to CRPC remains unclear. However, it is apparent that AR plays a pivotal role in this alteration. The recent discovery that microRNAs (miRNAs) can target the function of AR suggests a functional role of these non-coding RNAs in the pathogenesis of prostate cancer. miRNAs usually function by targeting the 3′ untranslated region (UTR) of a mRNA by base-pairing interactions and modulate translation either by destabilizing the message or by repression of protein synthesis in actively translating ribosomes. Here, we discuss the potential molecular pathways through which AR targeting miRNAs may promote CRPC. Modulation of AR expression by miRNAs presents a novel therapeutic option for prostate cancer, albeit it will likely be used in combination with the existing therapies.

Keywords

Androgen receptor; miRNA; 3′-UTR; Prostate cancer; miRNA therapeutics

Introduction

Prostate cancer continues to be the most common cancer diagnosed and the second leading cause of cancer-related deaths among older men in the United States. Despite early diagnosis and improvement in treatment modalities, several thousand men continue to die from the disease due to its aggressive behavior and distant organ metastases (1). The first line of treatment for patients with metastatic prostate cancer is androgen ablation therapy. While most patients with prostate cancer initially respond to androgen ablation therapy, the disease eventually relapses with castration-resistant prostate cancer (CRPC) within three years (2). At present, the underlying molecular mechanisms leading to CRPC are not clear and consequently, treatment of CRPC is only palliative (3). Understanding the molecular

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mechanisms, which promote advanced stage metastatic prostate cancer, could pave the way for the identification of novel therapeutic targets and development of effective management strategies for the disease.

Among the many genes implicated in the disease, the androgen receptor (AR) has emerged as the main contributor to prostate carcinogenesis. The AR protein is a ligand-dependent transcription factor, which belongs to the nuclear hormone receptor superfamily (4). The physiological ligands for AR include the androgens, testosterone and dihydrotestosterone. Upon activation by the binding of androgens, AR undergoes rapid homodimerization and nuclear translocation, and binds to specific DNA sequences termed androgen-responsive elements (AREs) located in the promoter regions of its target genes. After binding to promoters, AR recruits the coregulators, together with the basal transcriptional machinery, and modulates the transcription of its target genes (5–7) (Fig. 1). This AR signaling axis is required for the growth and development of a normal prostate gland and it appears to play a key role in all phases of prostate cancer, from disease initiation to disease progression and the development of CRPC (6, 8). Hence, AR emerges as the only significant target for the treatment of prostate cancer by the classical hormonal blockade therapy (3, 9). The therapy mainly involves the use of gonadotropin releasing hormone (GnRH) agonists and anti-androgens. The GnRH agonists function by suppressing testicular androgen synthesis and anti-androgens are designed to inhibit the binding of androgen to the ligand binding domain of AR (3, 9). In the initial androgen-dependent phase of prostate cancer, these agents repress AR activity and initiate tumor regression. However, after a short remission period, aberrant expression of AR occurs even in the presence of these therapies leading to the development of CRPC. The molecular mechanisms that are believed to facilitate the progression to AR-mediated CRPC include AR gene amplification, hypersensitivity of the AR to trace levels of circulating androgens, promiscuous affinity of the AR due to accumulation of numerous mutations and finally, growth factor-activated aberrant pathways, which are exclusively mediated via AR molecular actions (9–11). The most interesting and perhaps the principal mode for the development of CRPC is the subtle elevation in AR expression, which appears to promote the conversion of antagonist to agonist by altering the assembly of co-activators (12).

Overexpression of AR is a common aberration detected in CRPC (13–15). Chen et al.(12) have shown that AR overexpression is necessary and sufficient to transform androgen-dependent prostate cancer to CRPC in xenograft models. Elevated AR expression as modest as three-fold could promote CRPC by sensitizing the cells to low levels of ligand (12). However, the molecular basis for upregulation and stability of AR in prostate cancer cells is not well characterized. AR gene amplification has been reported in a minority (20–30%) of CRPC patients (13) and hence, it alone cannot account for the increased expression of AR observed in CRPC. Molecular mechanisms other than AR gene amplification seem to be important in the majority of AR-overexpressing castration-resistant tumors (14). It is plausible that the elevated AR expression is a consequence of the loss of expression of AR-targeting regulatory microRNAs (miRNAs). In addition, loss of miRNA binding sites in the truncated versions of the 3′ untranslated region (UTR) of AR can also lead to the loss of miRNA-mediated repression and upregulation of AR in CRPC. Here, we explore these two putative miRNA-mediated molecular mechanisms in the development of CRPC.

The AR, miRNAs and CRPC correlation

Regulatory miRNAs are a class of non-coding RNAs, which bind to the 3′ UTRs of their target mRNAs to repress translation, thus fine-tuning protein synthesis and functional control of target gene expression (16). The identification of miRNAs from various human tissues revealed tissue- and developmental-stage specific miRNA expression (17).

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Numerous studies have provided evidence of dysregulation of miRNAs probably in all types of human cancers, highlighting their significance as prognostic and diagnostic markers. miRNAs can contribute to carcinogenesis by acting as tumor suppressors or oncogenes (18). Deregulated expression of miRNAs in cancer cells can result due to genomic abnormalities such as chromosomal rearrangements, genomic amplifications and deletions of miRNA genes, and also due to altered transcriptional and post-transcriptional control of miRNA expression (19). In addition, epigenetic changes, such as methylation of CpG islands in the promoter regions of miRNA genes can alter miRNA expression in cancer cells (19, 20). An extensive analysis of miRNA genes has shown that about half of them are associated with CpG islands suggesting their possible regulation by DNA methylation machinery (21). Evidences for both, the silencing of miRNA expression by hypermethylation and overexpression by hypomethylation, have been described in tumorigenesis (22).

Aberrant expression of multiple miRNAs has been reported in prostate cancer. Several miRNAs, including miR 221, miR 222, miR 125b, miR 126*, miR 146a, miR 330, miR 449a and miR 148a were found to target the expression of growth regulatory genes in prostate cancer (23– 29). miR 331-3p has been shown to indirectly inhibit AR signaling pathway in prostate cancer cells by downregulating the expression of ERBB-2 tyrosine kinase receptor (30). A few androgen-regulated miRNAs, including miR 21 and miR 141 have also been identified (31, 32). Although the role of miRNAs in the development of AR-mediated CRPC has been hypothesized, the direct involvement of miRNAs through the regulation of AR function has not been established. The recent discovery that AR is a target of miRNAs provides evidence for miRNA-mediated AR regulation that could be crucial for the development of CRPC (33, 34). It is possible that prostate cancer cells, which are exposed to androgen blockade therapy acquire molecular alterations to promote hypermethylation of cancer cell genome. Such molecular reprogramming of genomic hypermethylation is likely to silence the expression of various tumor suppressing genes, including AR-targeting miRNA genes. Under typical cellular conditions, the expression of AR-targeting miRNAs modulates the expression of the receptor for proliferative turn-off (Figure 1). However, the loss of expression of AR-targeting miRNAs due to hypermethylation or other aberrant genomic alterations has the potential to promote increased AR expression, thus adding selective advantage to cancer cell proliferation (Figure 1). It is noteworthy that three-fold AR protein upregulation sensitizes the cells to CRPC (12). Interestingly, miRNAs appear to fine-tune their target gene expression by two- to four-fold (35, 36). Consequently, the increase in AR levels by loss of miRNA-mediated regulation has significant potential to favor the transition of prostate cancer to CRPC.

3’-Untranslated region of androgen receptor: another piece of AR-mediated CRPC puzzle

The 3′ UTR appears to play important roles in metazoan gene expression. It contains a wide variety of regulatory elements including polyadenylation signals, RNA binding protein motifs etc., which promote posttranscriptional control of gene expression. The human AR mRNA has a relatively long yet poorly characterized 3′ UTR. Genome sequence databases including GenBank and UCSC genome browser show 436 nucleotides long 3′ UTR of AR (NM_000044). However, studies provide evidence for 6.6 to 6.8 kb long 3′ UTR (34, 37, 38). Although the long AR 3′ UTR might suggest posttranscriptional regulation by RNA binding proteins and miRNAs, only limited information is available on this front. RNA binding proteins, such as poly (C)-binding protein-1 (CP-1), CP-2, Hu protein R (HuR) and ErbB3 binding protein 1 (EBP1) interact with the AR 3′ UTR (39, 40). However, the potential role of these proteins in the posttranscriptional regulation of AR expression in normal as well as prostate cancer cells remains uncharacterized. Since 3′ UTR of a mRNA is the main site of action of miRNAs, longer 3′ UTRs are likely to be targeted by multiple

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miRNAs. However, the importance of miRNAs in the regulation of 6.8 kb long AR 3′ UTR is largely unexplored except for the two recent studies (33, 34).

Most mammalian mRNAs are targets of miRNAs suggesting that miRNAs may have a significant impact on the evolution of 3′ UTRs. The 3′ UTRs appear to be under selective pressure to acquire or eliminate potential miRNA target sites (41, 42). miRNA-dependent repression could be detrimental to genes that are involved in basic cellular processes required for cell survival. Hence, these genes have evolved to have short 3′ UTRs in order to avoid miRNA target sites and escape miRNA-mediated translational repression (41). On the other hand, miRNA target genes are under selective evolutionary pressure to maintain long 3′ UTRs with high density of miRNA binding sites (41). AR mRNA has evolved with a long 3′ UTR presumably to be under the control of “evolutionarily favored” regulation by combinatorial action of multiple miRNAs. Further, since the shortening of 3′ UTRs seems to be a selective mechanism for avoiding miRNA regulation, it would be interesting to investigate the requirement of AR 3′ UTR length in different stages of prostate cancer.

Do several isoforms of AR mRNA differing in 3′ UTR lengths exist in different stages of prostate cancer? A recent study reported the widespread shortening of 3′ UTRs in cancer cells indicating the role of short 3′ UTRs in the activation of oncogenes (43). The mRNA isoforms with shorter 3′ UTRs were found to exhibit increased stability and produce ten-fold more protein partly due to the loss of miRNA-mediated repression (43). The LNCaP prostate cancer cell line appears to express two AR mRNA species of 8.5 kb and 11 kb (37, 44). The 8.5 kb AR mRNA lacked a region of 3′ UTR that was present in 11 kb AR mRNA isoform (37). We put forth the possibility of AR 3′ UTR being a dynamic region, with an inherent capacity to alter length, either at transcriptional or posttranscriptional levels utilizing multiple optimal and suboptimal polyadenylation sites to circumvent miRNA-dependent regulation. In addition to the loss of expression of AR-targeting miRNAs, the shortening of AR 3′ UTR leading to loss of miRNA binding sites may also contribute to the overexpression of AR in CRPC (illustrated in Figure 1). Hence, a comprehensive analysis of AR 3′ UTR and its roles in prostate cancer cells warrants further investigation.

Androgen receptor modulation by miRNAs: a much needed therapeutic opportunity

Despite the significance of AR in the development of CRPC and the established roles of miRNAs in carcinogenesis, the studies investigating a direct miRNA and AR functional connection have lagged behind. Evidence for miRNA-mediated regulation of AR is just beginning to emerge. miR 488* was found to directly target AR by binding to its specific site in the AR 3′ UTR (33). Immunoblot analysis showed that miR 488* can effectively downregulate AR protein expression in both androgen-sensitive and androgen-refractory prostate cancer cells. In addition, inhibition of cellular growth and increase in apoptosis was observed in miR 488* transfected cancer cells, indicating the therapeutic potential of miR 488*(33). Subsequent to the above report, another recent study conducted a tour de force gain-of-function screen of 1129 miRNAs to discover AR-regulating miRNAs in prostate cancer cell lines (34). Seventy one unique miRNAs that influenced AR protein levels were identified (34). A few AR-targeting miRNAs were found to decrease androgen-dependent proliferation of prostate cancer cells, again demonstrating the potential application of miRNAs in prostate cancer therapy (34).

Given the inadequate treatment strategies available for CRPC, the discovery of AR-targeting miRNAs is an important milestone in the field of prostate cancer. Despite the improvements being made in prostate cancer therapy, CRPC continues to have a fatal prognosis (3). The treatment options for CRPC are limited mainly by the incomplete knowledge regarding the

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molecular mechanisms leading to the development of CRPC. Prostate cancer cells challenged by the initial AR blockade therapy evolve multiple pathways to re-activate AR and become castration-resistant (9–11). Thorough understanding of the mechanisms underlying CRPC will open the door for better, innovative therapies. The miRNA-dependent regulation of AR reveals another possible mechanism for the development of CRPC. Hence, a rigorous investigation of the long AR 3′ UTR and AR-targeting miRNAs is certainly in place. Future investigations may unravel novel therapeutic targets, such as, factors involved in the processing of AR-targeting miRNAs or modulating the interaction of miRNAs with AR 3′ UTR or factors involved in the shortening/stability of AR 3′ UTR. Since CRPC results from the activation of multiple pathways, a single treatment strategy would be insufficient to combat CRPC. Hence, an approach based on a combination of therapies involving the simultaneous targeting of many pathways has gained acceptance as a treatment option for CRPC. Turning on the expression of AR-targeting miRNAs could prove to be a useful strategy for silencing AR in combination with the existing therapies. While the current therapies attempt to block already synthesized AR protein (3, 11, 45), miRNAs would target and destabilize AR mRNA and hence, could potentially improve the AR repression. Further, multiple AR-targeting miRNAs when used in combination for the suppression of AR could have a multiplicative effect and produce a more potent repression of AR as compared to a single miRNA.

Conclusions

The Nobel Prize winning discovery by Huggins and Hodges demonstrating that the androgen deprivation therapy produced prostate cancer remission in most men has remained the mainstay of therapeutic approaches (46). Nevertheless, recent findings convincingly demonstrate that AR continues to express in CRPC. Traditionally, small molecule inhibitors have been used to target the AR protein with limited success in retarding the progress of prostate cancer to metastatic stages. Therefore, a combinatorial therapeutic approach involving the assault of AR expression at protein level using traditional drugs as well as at RNA level by miRNAs provides a significant opportunity to treat advance stage cancer patients. The recent finding of multiple miRNAs targeting the long AR 3′ UTR suggests that miRNAs need to be considered as one of the players by which prostate cancer cells regulate AR levels. A detailed analysis of this potential AR-miRNA pathway in prostate cancer may reveal novel therapeutic targets for the treatment of CRPC.

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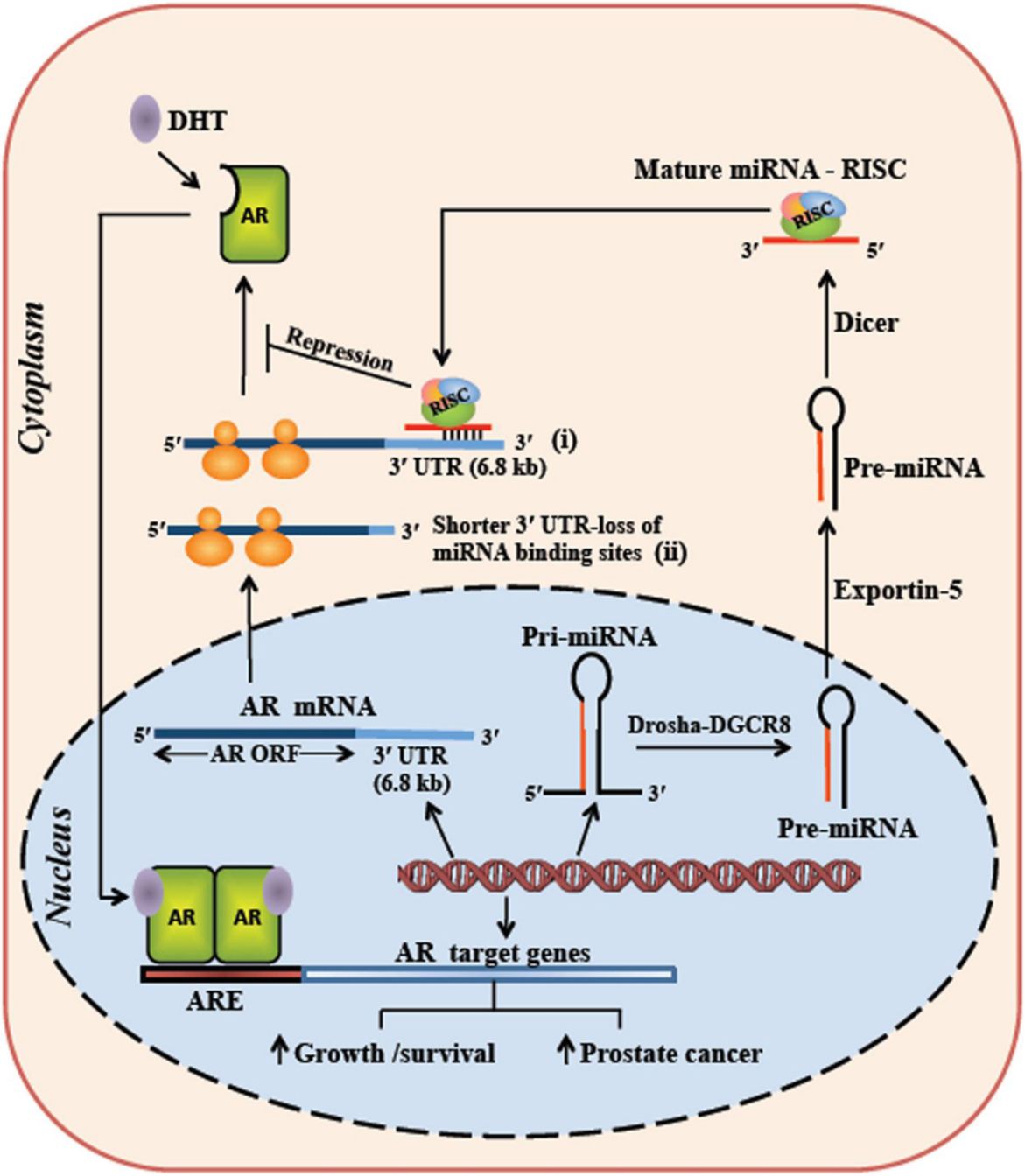


Figure 1. Potential AR-miRNA axis

The disruption of AR-miRNA axis may contribute to the development of prostate cancer. The potential mechanisms (i and ii) for the disruption of AR-miRNA axis are illustrated. After binding of its ligand, dihydrotestosterone (DHT), AR undergoes homodimerization and nuclear translocation. In the nucleus, AR modulates the transcription of its target genes by binding to the androgen-responsive elements (AREs) located in the promoters. The activation of target genes is required for the normal functioning of the prostate gland as well as for the progression of prostate cancer. The overexpression of AR has been implicated in the development of CRPC. AR-targeting miRNAs, presumably maintain optimal levels of AR by negatively regulating its expression. miRNAs are transcribed from the genome as

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primary (pri) miRNAs and processed into shorter RNA molecules (pre-miRNA and mature miRNA) by Drosha-DGCR8 in the nucleus and Dicer in the cytoplasm. Mature miRNAs together with the RNA-induced silencing complex (RISC) bind to the partially complementary sequences in the 3′ UTRs of their target mRNAs leading to translational repression or destabilization of mRNAs. The loss of AR-targeting miRNAs can potentially lead to elevated AR expression and contribute to the development of CRPC (i). In addition, shortening of AR 3′ UTR may occur by alternative splicing or alternative polyadenylation leading to the loss of miRNA binding sites. This molecular alteration would potentially disrupt miRNA-dependent repression of AR leading to AR overexpression, a cause for CRPC (ii). The genomic DNA shown in the figure is for illustration purposes only – the AR gene, the AR-targeting miRNA gene and AR target genes are not necessarily located in the adjacent loci.